Hailey-Hailey Disease Is Not Allelic to Darier's Disease

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Hailey-Hailey (Familial Benign Chronic Pemphigus) Disease is a rare autosomal dominant disorder characterized by blisters caused by suprabasal epidermal acantholysis. Another autosomal dominant skin disease, Darier's disease, has clinical and histologic features which overlap those of Hailey-Hailey disease and recently has been mapped to chromosome 12q23-q24.1. We have used linkage analysis to test whether or not a mutation in this region might also underlie Hailey-Hailey disease. This analysis, using polymorphic loci tightly linked to Darier's disease, excluded this region as the site for the disease-causing mutation in two kindreds affected with Hailey-Hailey disease. *J Invest Dermatol 102:992–993, 1994*

Hailey-Hailey disease, first described in 1939, most commonly presents in the second to fourth decade of life with skin fragility and uncomfortable lesions in the flexures or at the sites of trauma [1–3]. These lesions begin as clear vesicles and progress to erosion and crusts that may be misdiagnosed as eczema or infections with bacteria or fungi. Histologically there is characteristic lesional suprabasal acantholysis, and ultrastructurally there is a breakdown of desmosome-keratin filament complexes in established lesions [4–6]. The pathogenesis of this autosomal dominantly inherited skin disease remains unclear.

We are attempting to find the genetic mutation underlying Hailey-Hailey disease by using linkage analysis to compare the inheritance of the disease with the inheritance of chromosomal regions known to contain "candidate" genes that are involved in keratinocyte cohesion and differentiation.

The inheritance of another rare autosomal dominant skin disorder, Darier's disease, recently has been linked to the inheritance of polymorphic loci at 12q23-q24.1 [7–9] (Ikeda *et al,* submitted). Because of these recent findings and the clinical and histologic overlap between these two genodermatoses [4,10], we assessed whether the Hailey-Hailey gene also might lie in this region. We report here evidence against the contribution of gene mutations in this region to the underlying pathogenesis of Hailey-Hailey disease, thus confirming genetically the general clinical conclusion that Darier's and Hailey-Hailey diseases are distinct entities.

MATERIALS AND METHODS

Subjects We studied two families with multiple members affected with Hailey-Hailey disease (Fig 1). All affected individuals had clinical features characteristic of Hailey-Hailey disease. In pedigree Bo, the diagnosis of Hailey-Hailey disease was confirmed by skin biopsy in most affected members. The average age of onset in pedigree Bo was 25 years, with a range of 20 to 40 years of age. The family members considered to be unaffected were over 40 years old. In pedigree Ma, Hailey-Hailey disease was confirmed histologically in several family members. The average age of onset in this pedigree was 26 years with a range of 17 to 45 years of age.

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Genotyping and Linkage Analysis Peripheral blood samples from 47 individuals (27 affected, 20 unaffected) were obtained after informed consent, and DNA was extracted using standard techniques [11]. Polymorphic loci used for linkage were analyzed by Southern blotting of restriction fragment length polymorphisms or by electrophoresis on denaturing polyacrylamide gels of radio-labeled, polymerase chain reaction (PCR) products amplified from loci containing microsatellite repeats [12]. Two-point linkage analysis was calculated with LIPED [13].

RESULTS

Linkage analysis comparing the inheritance of Hailey-Hailey disease with the inheritance of two chromosome 12q23-q24.1 polymorphic loci, D12S79 and D12S84, estimated to lie 6cM apart [12] and known to flank the Darier's disease gene (Ikeda *et al,* submitted) provided strong evidence against this region being the site of the mutation underlying Hailey-Hailey disease in these two kindreds (Table I).

In addition, we also have compared the inheritance of Hailey-Hailey disease with the inheritance of chromosomal regions known to contain genes that are involved in epidermal cohesion and differentiation. These candidate genes include types I and II keratin genes (chromosomes 17q and 12q, respectively), loricrin (1q), desmoplakin I/II (6p), CD44 (11p), and several desmosomal proteins (6p, 7, 9p, and 18). Evidence against mutations in these regions in the two families studied (data not shown) has led us to begin a genome-wide scan, and we have examined a total of 94 polymorphic loci; the results of these studies so far have all been negative.

DISCUSSION

Our findings are conclusive evidence against linkage between Hailey-Hailey disease and markers in the chromosome 12q23-q24.1 region that has been tightly linked to Darier's disease. Therefore, despite their clinical overlap, Darier's disease and Hailey-Hailey disease result from mutations in different genes. Our evidence does not, however, preclude a mutation in a gene related to, but in a location separate from, the putative gene defect responsible for Darier's disease.

Studies identifying abnormalities in the desmosomal-keratin filament complex in Hailey-Hailey disease [14] suggest that mutations encoded by proteins of this complex might be the primary pathogenic signal in Hailey-Hailey disease. Whereas our studies have excluded sites where many of these genes have been mapped, the chromosomal locations of other components have not been reported, and there may be additional proteins not yet identified.

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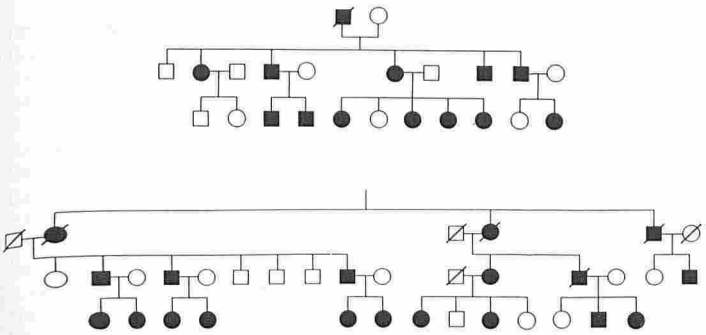

Figure 1. Pedigrees used for linkage analysis. Family members with a diagnosis consistent with Hailey-Hailey disease *(solid symbols)*. Unaffected family members *(open symbols)*. *Upper,* Bo family; *lower,* Ma family.

Table I. Pairwise Lod Scores Between Hailey-Hailey Disease and D12S84 and D12S79[a]

	Lod Score at θ of				
Locus Family	0	0.01	0.05	0.10	0.20
D12S84					
Bo	$-\infty$	−11.07	−6.45	−4.27	−2.15
Ma	$-\infty$	−7.66	−3.66	−2.04	−0.67
D12S79					
Bo	$-\infty$	−13.51	−7.34	−4.80	−2.43
Ma	$-\infty$	−4.92	−2.34	−1.32	−0.44

[a] Paternal and maternal segregation are combined, and autosomal dominant inheritance with full penetrance and no sporadic cases have been assumed.

Further linkage studies will be required to define the disease gene that disrupts the cohesion between keratinocytes and leads to faulty epidermal function in Hailey-Hailey disease.

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